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(54)【発明の名称】　ポリスルホン系選択透過膜

(57)【要約】

【目的】　性能劣化や血小板の活性化が起こりにくいポリスルホン系選択透過膜を提供する。

【構成】　ポリスルホン系ポリマーと親水性ポリマーとから成る選択透過膜に於いて、該膜が凝集粒子の集合体から成り、しかも凝集粒子の表面に親水性ポリマーが濃縮しているポリスルホン系選択透過膜、その際親水性ポリマーがポリビニルピロリドンであること、凝集粒子の表面に濃縮している親水性ポリマーの濃度が２５～５０重量%であること、膜における緻密層が直径１０～１００ｎｍの凝集粒子から成ること、水系に於けるオボアルブミンの透過率が４０～８０％であり、かつ牛血漿系に於けるアルブミンの透過率が１．０%以下であるポリスルホン系選択透過膜。

【特許請求の範囲】

【請求項１】　ポリスルホン系ポリマーと親水性ポリマーとから成る選択透過膜に於いて、該膜が凝集粒子の集合体から成り、しかも凝集粒子の表面に親水性ポリマーが濃縮していることを特徴とするポリスルホン系選択透過膜。

【請求項２】　親水性ポリマーがポリビニルピロリドンであることを特徴とする請求項１記載のポリスルホン系選択透過膜。

【請求項３】　凝集粒子の表面に濃縮している親水性ポリマーの濃度が２５～５０重量%であることを特徴とする請求項１記載のポリスルホン系選択透過膜。

【請求項４】　膜における緻密層が直径１０～１００ｎｍの凝集粒子から成ることを特徴とする請求項１記載のポリスルホン系選択透過膜。

【請求項５】　水系に於けるオボアルブミンの透過率が４０～８０%であり、かつ牛血漿系に於けるアルブミンの透過率が１．０%以下であることを特徴とする請求項１記載のポリスルホン系選択透過膜。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は血漿分析分野で用いられる中空糸状のポリスルホン系選択透過膜に関する。

【０００２】

【従来の技術】従来、血液透析の分野では製膜時に膜の透析性能の制御がしやすく、また生体適合性に優れるという理由から合成ポリマーを素材とする中空糸膜が幾つか実用化されている。その中でも機械的強度と化学的安定性を兼ね備えた膜として、ポリスルホン系中空糸膜が広く使われ始めている。ところが、膜素材がポリスルホン系ポリマー単独から成る場合は表面の親水性が著しく不足するため、血漿蛋白の吸着が起こりやすい。その結果、膜の空孔部での目詰まりによる膜の性能劣化が起こってしまう。しかも親水性が不足するとプライミング時の気泡の抜けが悪く、膜中に残った気泡が血液中へ徐々に抜け出して血小板を活性化するため、血小板粘着を起こして血漿凝固に至りやすいという欠点があった。この様にポリスルホン系ポリマー単独では血液透析膜を得ることが困難であり、親水性ポリマーをポリスルホン系ポリマーにブレンドする等の方法で親水化することが考えられた。

【０００３】ポリスルホン系ポリマーの親水化に関しては、主に透水性の向上を目的として種々の方法が考えられてきたが、親水性ポリマーの溶出を最小限に抑制し、かつ十分な親水性を得る方法として以下の二例が開示されている。特開昭６２－３８２０５号公報には膜の緻密層側だけに親水性ポリマーが存在する膜が開示されているが、医療用途まで開示されていない。さらに特開平４－３００６３６号公報には中空糸膜の内表面近傍に親水性ポリマーが膜に片側だけに偏在した膜が開示されている。ところが、この膜では親水性ポリマーが膜の片側だけに偏在しているため、それ以外の部分で血漿蛋白の吸着が起こってまくの性能劣化が起こりやすく、また気泡の抜けも悪く、従って、血小板の活性化をおこしやすいと考えられる。

【０００４】

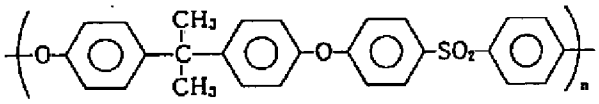
【発明が解決しようとする課題】本発明は性能劣化や血小板の活性化が起こりにくいポリスルホン系選択透過膜を提供するものである。

【０００５】

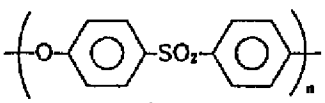
【課題を解決するための手段】前記課題を解決するために鋭意検討した結果、本発明でえられるポリスルホン系選択透過膜は、膜を形成する全ての凝集粒子表面が均一に親水化されているため、膜の性能劣化や血小板の活性化がおこりにくいことを見出した。本発明の膜を形成する第一の素材はポリスルホン系ポリマーであり、下記の化学式（１）、または（２）で示されるポリマーであるが、芳香族の官能基やアルキル基が導入されたいわゆる変性ポリスルホンでもよく、特に限定はない。

【０００６】

【化１】



…… (1)



…… (2)

【０００７】第二の素材は親水性ポリマーであり、ポリスルホン系ポリマーと相溶化するものであれば良く、代表例としてポリビニルピロリドンが挙げられる。他にはビニルピロリドンと他のビニル系モノマーとの共重合体やポリエチレングリコール等が挙げられるが、個々の凝集粒子の表面には親水性ポリマーが均一な濃度に濃縮されている。

【０００８】親水性ポリマーの濃度は、低すぎると凝集粒子表面の親水性が不足するため、血漿蛋白の吸着がおこって膜の性能劣化をひきおこし、また、プライミング時の気泡の抜けが悪く、血小板の活性化をおこしやすくなる。反対に、濃度が高すぎるとポリスルホン系ポリマ

ーとの絡み合いが不十分になり、水中への溶出量が増加するため医療用途として好ましくない。従って、凝集粒子表面の親水性ポリマー濃度は２５～５０重量%が好ましく、２５～３５重量%がさらに好ましい。ここで用いる親水性ポリマー濃度とは、中空糸表面に露出している凝集粒子表面をＸ線で走査し、得られた光電子スペクトルがら構成元素の平均濃度を求め、その値を下記式（３）に代入して算出した値である。

【０００９】

【式１】

$$\text{親水性ポリマー濃度（重量%）} = \frac{C_1 \times M_1}{C_1 \times M_1 + C_2 \times M_2} \times 100 \quad \cdots\cdots (3)$$

C_1 ：含窒素親水性ポリマーの含有率合いは窒素原子濃度（%）、ポリエチレングリコールの場合はカルボニル基の炭素原子濃度（%）

C_2 ：イオウ原子濃度（%）

M_1 ：親水性ポリマーの繰り返しユニットの分子量

M_2 ：ポリスルホン系ポリマーの繰り返しユニットの分子量

【００１０】本発明の膜はこの様な凝集粒子の集合体であり、血液との接触面側に緻密層を、それ以外の部分では支持層を有している。緻密層は透過性能を決定する部分であり、重要な因子として緻密層を形成している凝集粒子の大きさを挙げることができる。一般的には緻密層を形成している凝集粒子の直径が小さく、しかも蜜に集合するほど膜の透過性能は低くなる。反対に、大きすぎても有用な血漿蛋白であるアルブミンが透過してしまい、血液透過膜としては好ましくない。

【００１１】最近の血液透過療法では、透析アミロイド症状の改善のために原因物質とされているβ２－マイクログロブリン（分子量：１１，８００）を十分に透過させるが、アルブミン（分子量：６７，０００）はほとんど透過させない分画性を有する膜が求められており、この様な透過性能を発現させるには緻密層の凝集粒子の大きさを制御する必要がある。凝集粒子の大きさは中空糸断面部の電子顕微鏡写真から平均直径として算出するもので、直径が１０～１００ｎｍ、好ましくは１０～５０ｎｍである。

【００１２】本発明の血液透析膜は、水系におけるオボアルブミン（分子量：４７，０００）の透過率が４０～８０%であり、かつ牛血漿系におけるアルブミンの透過率が１．０%以下という特徴を有するが、これらは実際の血液透析においてβ２－マイクログロブリンの透過率が６０～７０%、アルブミンの透過率が０．３%以下というレベルに相当している。支持層は膜の機械的強度を支配しているを考えられるが、十分な膜強度が得られればよく、支持層における凝集粒子の大きさやその集合形態に関しては特に限定はない。

【００１３】次に、上記特徴を有する中空糸膜の実施態様の一例として、親水性ポリマーにポリビニルピロリドン（以下「ＰＶＰ」という。）を用いる場合について説明する。製膜原液の組成としてはポリスルホン系ポリマーが１０～２０重量%、ＰＶＰが２～８重量%、およびこれらの溶剤から成る。溶剤はポリスルホン系ポリマーとポリビニルピロリドンとを溶解できるものであればよく、Ｎ，Ｎ－ジメチルアセトアミド（以下「ＤＭＡＣ」という。）、Ｎ，Ｎ－ジメチルホルムアミド、Ｎ－メチル－２－ピロリドン、ジメチルスルホキシド等が列挙され、これらを単独、あるいは任意の割合で混合して使用することができる。さらにポリスルホン系ポリマーの非溶剤として、ポリマーが析出しない程度に水を添加してもよい。

【００１４】製膜過程においては、製膜原液からの溶剤の拡散と非溶剤の侵入により、ポリスルホン系ポリマーの核形成の後、凝集粒子が生成するが、その際親水性ポリマーは凝集粒子の外側へ拡散し、凝集粒子から抜け出していくと考えられる。そこで、親水性ポリマーが完全に抜けきらないうちに凝集粒子の凝固を完了させると、生成した凝集粒子表面に親水性ポリマーが濃縮される。従って、ＰＶＰを好ましい濃度で凝集粒子表面に濃縮させるには、生成過程にある凝集粒子内のＰＶＰの拡散速度を制御する必要があり、以下の詳述する因子で制御できる。

【００１５】第一の制御因子は製膜原液中のＰＶＰの分子量である。即ち、ＰＶＰの分子量が小さすぎる場合は、凝集粒子の生成が終了しないうちにＰＶＰは凝集粒子外へ速やかに拡散してしまい、凝集粒子表面に所望の濃度で濃縮されない。反対に、分子量が大きい場合、ポリスルホン系ポリマーの絡み合いが大きくなるためＰＶＰの拡散速度が遅くなり、濃縮されやすく、また分子量が大きいほど凝集後もポリスルホン系ポリマーとの絡み合いが強固となるため表面からの溶出も抑えられる。従って、好ましい分子量は２０～５０万であり、これ以上大きいと製膜原液の粘度が高すぎて紡糸性が悪くなる。さらに好ましい分子量は３０～４０万である。

【００１６】第二の制御因子は中空剤の組成である。中空剤は、製膜原液における凝集粒子の生成速度とＰＶＰの拡散速度とを制御できる組成が好ましく、溶剤の水溶液が用いられるが、同時にＰＶＰを含有してもよい。これは吐出直後に中空剤中のＰＶＰが製膜原液中へ速やかに拡散し、製膜原液中から拡散しようとするＰＶＰと十分な濃度平衡を形成した状態で凝集粒子の生成を完了させれば、凝集粒子表面に所望の濃度でＰＶＰを濃縮させることができるからである。従って、製膜原液中のＰＶＰよりも拡散速度が大きいほうが好ましく、より小さい分子量のものが用いられる。好ましい分子量は０．５～

５万である。また、添加量を増やすに従って製膜原液中のＰＶＰの拡散速度を遅らせることができるが、添加量が多くなると膜の凝固速度が遅くなり紡糸性が悪くなる。従って、好ましい添加量は１０～３０重量%である。

【００１７】中空剤に添加される溶剤は凝集粒子の生成速度と膜の透過性能を制御する目的で用いられ、性膜原液と同一、あるいは異なる組成であり、添加量を増やすに従って凝集粒子の生成速度は遅くなり、しかも粒子径を大きくすることができる。中空剤から拡散するＰＶＰと凝集粒子から拡散するＰＶＰが十分に濃度平衡に達した状態で、凝集粒子の生成を終了させるのに好ましい溶剤の添加量は０～６０重量%であり、これ以上添加量が多いと形成された膜はアルブミンを透過してしまう。さらに好ましくは３０～５０重量%である。

【００１８】第三の制御因子は温度である。上記の製膜原液と中空剤とは環状オリフィスを有する紡糸口金から同時に吐出され、空中走行の後、凝固浴中へ導かれる。このさいＰＶＰの拡散速度は製膜原液、中空剤および空中走行部の温度によっても制御できる。これらを高温にするほどＰＶＰの拡散を速めることができるが、高すぎると製膜原液の粘度が低下し、また膜の凝固速度も遅くなるため紡糸性が悪くなる。反対に低温にするほどＰＶＰの拡散速度を遅らせることができるが、低すぎると膜の凝固が速く、ＰＶＰが凝集粒子表面層に濃縮されない。従って、製膜原液の好ましい温度は３０～８０℃であり、さらに好ましくは３５～６０℃である。中空剤の温度は製膜原液と同一とする。また空中走行部の温度は製膜原液の温度と極端に異なると、紡糸性が悪くなるため、製膜原液と同様に３０～８０℃に設定し、さらに好ましくは３５～６０℃である。凝固浴は膜の凝固を完了させる以外に、溶剤や余分のＰＶＰを除去させる目的で用いられ、好ましい温度は４０～６０℃である。

【００１９】この様に凝固させた中空糸膜をカセに巻取り、一定長に切断した後、カセットに挿入する。束の切断面上方より熱水シャワーをふらせ、中空糸の内側、外側、および断面部を洗浄し、さらに余分のＰＶＰを除去させる。最後にグリセリン水溶液を付着させて乾燥すれば本発明の中空糸膜が得られる。

【００２０】

【実施例】次に、本発明を実施例にて具体的に説明するが、本発明はそれらにより何ら限定されるものではない。なお、実施例で用いられている諸数値は以下の手順にて測定したものである。

（凝集粒子の直径）電界放射型走査電子顕微鏡にて凍結割断面の写真（倍率；７０，０００倍）を撮影し、緻密層の最表層の凝集粒子の平均直径を算出した。

（膜中のＰＶＰ濃度）中空糸を流水中（水温；１５～２０℃）に一昼夜浸漬し、付着しているグリセリンを洗浄した。１０５℃で絶乾したにち元素分析で膜中の窒素濃度を求め、ＰＶＰ濃度に換算した。

【００２１】（凝集粒子表面のＰＶＰ濃度）Ｘ線光電子スペクトル測定装置（ＰＨＩ－５４００型）を用いて、凝集粒子表面深さ６ｎｍまでの窒素およびイオウ原子の平均濃度を求め、これを式（３）に代入してＰＶＰ濃度を算出した。試料の調整法は以下の手順で行った。

内表面：長さ５ｍｍの中空糸を内表面が露出するように切開し、数本を試料台に隙間なく固定した。外表面：長さ５ｍｍの中空糸を内表面が露出するように切開し、数本を試料台に隙間なく固定した。

断面部：数十本束ねた中空糸膜を凍結割断し、割断面が上向きになる様に試料台に固定した。

【００２２】（中空糸膜への血小板の粘着）膜表面への粘着量を活性化の指標とした。長さ１５ｃｍの中空糸膜を１０本束ねて小型モジュールを作成し、該モジュールにヘパリン添加新鮮血を線速１．０ｃｍ／ｓｅｃにて１５分間通過させ、続いて生理食塩水を１分間通過させた。次に中空糸を細断し、０．５%トリトンＸ－１００を含む生理食塩水中で超音波照射して膜表面に粘着した血小板から放出される乳酸脱水素酵素を定量した。酵素活性の測定はＬＤＨモノテストキット（ベーリンガー・マンハイム・山之内社製）を使用した。

【００２３】（中空糸膜への血漿蛋白の吸着）長さ２０ｃｍの中空糸膜を１００本束ねて小型モジュールを作成した。このモジュールに３７℃に加温したヘパリン添加牛血漿（ヘパリン５０００ＩＵ／ｌ、蛋白濃度６．０ｇ／ｄｌ）を線速１．０ｃｍ／ｓｅｃで導入し、膜間圧力差５０ｍｍＨｇにおいて２４０分間限外濾過を行った後、生理食塩水で１分間洗浄した。次に中空糸膜を細断し、１．０%ラウリル酸ナトリウムを含む生理食塩水中で攪拌して抽出した血漿蛋白を定量した。蛋白濃度の測定はＢＣＡプロテインアッセイ（ピアース社製）を使用した。

【００２４】（水系でのオボアルブミン透過率測定）長さ２０ｃｍの中空糸膜を１００本束ねて小型モジュールを作成した。このモジュールに３７℃に加温したオボアルブミン水溶液（２５０ｐｐｍ）を線速１．０ｃｍ／ｓｅｃで導入し、膜間圧力差２５ｍｍＨｇにおいて３０分間限外濾過を行った。得られた濾液と元液の吸光度を波長２８０ｎｍで測定し、下記の式（４）に代入して透過率を算出した。

【００２５】

【式２】

$$\text{透過率（%）} = \frac{\text{濾液の吸光度}}{\text{元液の吸光度}} \times 100 \quad \cdots\cdots (4)$$

【００２６】（牛血漿系でのアルブミン透過率およびＵＦＲ測定）長さ２０ｃｍの中空糸膜を１００本束ねて小型モジュールを作成した。このモジュールに３７℃に加温したヘパリン添加牛血漿（ヘパリン５０００ＩＵ／ｌ、蛋白濃度６．０ｇ／ｄｌ）を線速１．０ｃｍ／ｓｅｃで通過させ、膜間圧力差５０ｍｍＨｇにおいて６０分間限外濾過を行った。アルブミンの透過率は通液開始後３０分目に濾液を採取し、得られた濾液と元液のアルブミン濃度を定量した後、下記の式（５）に代入して透過率を算出した。アルブミン濃度の測定はＡ／ＧＢ－テストワコー（和光純薬製）を使用した。ＵＦＲ測定は５、３０、６０分目に濾液を採取し、重量を測定して算出した。

【００２７】

【式３】

$$\text{透過率（％）} = \frac{\text{濾液のアルブミン濃度}}{\text{元液のアルブミン濃度}} \times 100 \quad \cdots\cdots (5)$$

【００２８】（溶出物）中空糸膜１．５ｇを水１５０ｍｌに入れ、７０℃で１時間加熱した。この上澄について波長２２０～３５０ｎｍの範囲で紫外線吸光度を測定した。

【００２９】（実施例１）ポリスルホン（ＡＭＣＯ社製：Ｐ－１７００）１６部とＰＶＰ（ＢＡＳＦ社製：Ｋ－９０、分子量３６万）４部をＤＭＡＣ８０部に添加して、５０℃で８時間攪拌、溶解し、製膜原液を得た。次に、ＤＭＡＣ４５部と水５５部とを混合して中空剤を得た。５０℃に保温した製膜原液、および中空剤を外型０．３ｍｍ、内径０．２ｍｍの環状オリフィスを有する紡糸口金から５０℃に保温した空中走行部に同時に吐出させ、吐出部の４５ｃｍ下方に設置した６０℃の凝固浴中を通過させた後、カセに巻取った。切断後、束の切断面上方から８０℃の熱水シャワーを２時間かけて洗浄し、グリセリン水溶液を付着させて真空乾燥した。得られた中空糸膜は膜性能の劣化や血小板の活性化がなかった。表－１に測定結果を示す。

【００３０】（実施例２）ＤＭＡＣ３０部とＰＶＰ（Ｋ－１５、分子量４万）３０部、および水４０部から成る中空剤を用いた以外は実施例１の条件に従った。得られた中空糸膜は膜性能の劣化や血小板の活性化がなかった。表－１に測定結果を示す。

【００３１】（比較例１）ＤＭＡＣ２５部と水７５部から成る中空剤を用い、さらに製膜原液と空中走行部の温度を２３℃に保温した以外は実施例の条件に従った。得られた中空糸膜は膜性能の劣化が激しく、血小板を活性化した。表－１に測定結果を示す。

【００３２】

【表１】

表－１	実施例１	実施例２	比較例１
膜中のＰＶＰ濃度（％）	6.8	7.0	6.2
凝集粒子表面のＰＶＰ濃度（％） 内表面 外表面 断　面	 33 35 31	 38 40 40	 20 19 20
凝集粒子直径（nm）	40	51	31
血小板粘着量（LDH-unit/cm-HF）	8.3	4.1	105.8
血漿蛋白吸着量（mg/g-HF）	2.8	2.1	66.4
水系オボアルブミン透過率　（％）	67.5	73.6	61.1
牛血漿系アルブミン透過率　（％）	0.3	0.8	0.7
牛血漿系ＵＦＲ（ml/mmHg·hr·m²） 5分目 30分目 60分目	 41 41 40	 43 44 43	 26 21 18
溶出物（ABS.max）	0.055	0.084	0.042

【００３３】

【発明の効果】本発明の組成物は膜性能の劣化や血小板の活性化がなく、血液透析用の選択透過膜として有用なものである。

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(54) POLYSULFONE-BASED SELECTIVE PERMEABLE MEMBRANE

(57)Abstract:
PURPOSE: To prepare a polysulfone-based selective permeable membrane less liable to the deterioration of performance and hardly activating blood platelets.
CONSTITUTION: When a selective permeable membrane is composed of a polysulfone polymer and a hydrophilic polymer, it is made of an aggregate of flocculated particles with the hydrophilic polymer concd. in the surfaces. Polyvinylpyrrolidone is used as the hydrophilic polymer, the concn. of the hydrophilic polymer concd. in the surfaces of the flocculated particles is regulated to 25-50wt.% and a dense layer in the membrane is made of flocculated particles each having 10-100nm diameter to obtain the objective polysulfone- based selective permeable membrane having 40-80% permeability to ovalbumin in a water system and ≤1.0% permeability to albumin in a cow blood plasma system.

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CLAIMS

[Claim(s)]
[Claim 1] Polysulfone system permselective membrane characterized by for this film having consisted of the aggregate of floc and moreover the hydrophilic polymer having condensed on the surface of floc in the permselective membrane which consists of a polysulfone system polymer and a hydrophilic polymer.
[Claim 2] Polysulfone system permselective membrane according to claim 1 characterized by a hydrophilic polymer being a polyvinyl pyrrolidone.
[Claim 3] Polysulfone system permselective membrane according to claim 1 characterized by the concentration of the hydrophilic polymer condensed on the surface of floc being 25 - 50 % of the weight.
[Claim 4] Polysulfone system permselective membrane according to claim 1 characterized by consisting of the floc whose compact layer in the film is the diameter of 10-100nm.
[Claim 5] Polysulfone system permselective membrane according to claim 1 characterized by for the transmission of the ovalbumin in a drainage system being 40 - 80%, and the transmission of the albumin in a cow plasma system being 1.0% or less.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the hollow filament-like polysulfone system permselective membrane used in the plasma analysis field.
[0002]
[Description of the Prior Art] Conventionally, in the field of hemodialysis, some hollow fibers made [are easy to carry out control of the membranous dialysis engine performance at the time of film production, and] from a synthetic polymer since it says that it excels in biocompatibility are put in practical use. As film which combines a mechanical strength and chemical stability also in it, a polysulfone system hollow fiber is beginning to be used widely. However, since surface hydrophilic properties run short remarkably when a film material consists of a polysulfone system polymer independent, adsorption of a plasma protein tends to take place. Consequently, the performance degradation of the film by the blinding in the membranous hole section will happen. And when hydrophilic properties ran short, the omission of the air bubbles at the time of a priming was bad, and in order that the air bubbles which remained into the film might slip out gradually into blood and might activate a platelet, there was a fault of having

started platelet adhesion and being easy to result in plasma coagulation. Thus, it is difficult to obtain the hemodialysis film and it was possible to carry out hydrophilization by the approach of blending a hydrophilic polymer to a polysulfone system polymer a polysulfone system polymer independent.

[0003] Although various approaches have mainly been considered for the purpose of permeable improvement about the hydrophilization of a polysulfone system polymer, the following two examples are indicated as an approach of controlling the elution of a hydrophilic polymer to the minimum, and acquiring sufficient hydrophilic property. Although the film with which a hydrophilic polymer exists only in a membranous compact layer side is indicated by JP,62-38205,A, it is not indicated to the medical-application way. Furthermore, the film with which the hydrophilic polymer was unevenly distributed in the film near the internal surface of a hollow fiber only at one side is indicated by JP,4-300636,A. However, by this film, since the hydrophilic polymer is unevenly distributed only in membranous one side, it is thought that taking place and winding [adsorption of a plasma protein]-in other part performance degradation tends to happen, and the omission of air bubbles is also bad, therefore tends to cause activation of a platelet.

[0004]

[Problem(s) to be Solved by the Invention] This invention offers the polysulfone system permselective membrane to which neither performance degradation nor activation of a platelet can take place easily.

[0005]

[Means for Solving the Problem] It found out that neither membranous performance degradation nor activation of a platelet could start easily the polysulfone system permselective membrane obtained by this invention as a result of inquiring wholeheartedly, in order to solve said technical problem since hydrophilization of all the floc front faces that form the film is carried out to homogeneity. Although the first material which forms the film of this invention is a polysulfone system polymer and it is the following chemical formula (1) or the polymer shown by (2), the so-called denaturation polysulfone into which the functional group and alkyl group of aromatic series were introduced is sufficient, and there is especially no limitation.

[0006]

[Formula 1]

[0007] The second material is a hydrophilic polymer and a polyvinyl pyrrolidone is mentioned as an example of representation that what is necessary is just a polysulfone system polymer and the compatibility-ized thing. Although a copolymer, a polyethylene glycol, etc. of vinyl pyrrolidone and other vinyl system monomers are mentioned to others, the hydrophilic polymer is condensed by uniform concentration in the front face of each floc.

[0008] Since the concentration of a hydrophilic polymer runs short of the hydrophilic properties on the front face of floc if it is too low, adsorption of a plasma protein starts, membranous

performance degradation is caused, and the omission of the air bubbles at the time of a priming is bad, and becomes easy to cause activation of a platelet. Since a tangle in a polysulfone system polymer will become inadequate and an underwater elution volume will increase on the contrary if concentration is too high, it is not desirable as a medical-application way. Therefore, the hydrophilic polymer concentration on the front face of floc has 25 - 50 desirable % of the weight, and its 25 - 35 % of the weight is still more desirable. The hydrophilic polymer concentration used here scans the floc front face exposed to a hollow filament front face through an X-ray, and is the value the obtained photoelectron spectrum asked for the average concentration of a ****** element, and computed by having assigned it to the following type (3).
[0009]
[Formula 1]

C1 : In the case of nitrogen atom (%) and concentration, and a polyethylene glycol, content **** of a nitrogen-containing hydrophilic-property polymer is the carbon atom concentration (%) of a carbonyl group.
C2 : Sulfur atom concentration (%)
M1 : Molecular weight M2 of the repeat unit of a hydrophilic polymer : Molecular weight of the repeat unit of a polysulfone system polymer [0010] The film of this invention is the aggregate of such floc, and has supporters for the compact layer in the other part in the contact surface side with blood. A compact layer is a part which determines penetrable ability, and can mention the magnitude of the floc which forms the compact layer as an important factor. The diameter of the floc which generally forms the compact layer is small, and membranous penetrable ability becomes low, so that it moreover gathers to nectar. On the contrary, even if too large, the albumin which is a useful plasma protein penetrates and it is not desirable as hemofiltration film.
[0011] Although the beta2-micro globulin (molecular weight: 11,800) made into the causative agent for the improvement of a dialysis amyloid symptom is made to fully penetrate, most albumin (molecular weight: 67,000) needs to control the magnitude of the floc of a compact layer by the latest hemofiltration therapy for the film which has the fractionation nature which is not made to penetrate to be called for, and make such penetrable ability discover. The magnitude of floc is computed as an average diameter from the electron microscope photograph of the hollow filament cross-section section, and 10-100nm of diameters is 10-50nm preferably.
[0012] Although the transmission of the ovalbumin (molecular weight: 47,000) in a drainage system is 40 - 80% and, as for the hemodialysis film of this invention, the transmission of the albumin in a cow plasma system has the description of 1.0% or less, these are equivalent to the level of [transmission / of a beta2-micro globulin] 0.3% or less in the transmission of 60 - 70%, and albumin in actual hemodialysis. Although supporters are governing the membranous mechanical strength and ** can be considered, about the magnitude and its set gestalt of the floc in supporters, there is especially no limitation that sufficient film reinforcement should just be obtained.
[0013] Next, the case where a polyvinyl pyrrolidone (henceforth "PVP") is used for a hydrophilic polymer is explained as an example of the embodiment of a hollow fiber which has the above-mentioned description. As a presentation of a film production undiluted solution, PVP consists [a polysulfone system polymer] of 2 - 8 % of the weight, and these solvents ten to 20% of the weight. That what is necessary is just what can dissolve a polysulfone system polymer and

a polyvinyl pyrrolidone, N,N-dimethylacetamide (henceforth "DMAC"), N.N-dimethylformamide, a N-methyl-2-pyrrolidone, dimethyl sulfoxide, etc. are enumerated, and a solvent can mix and use these at a rate of independence or arbitration. Furthermore, water may be added as nonsolvent of a polysulfone system polymer to extent in which a polymer does not deposit.

[0014] In a film production process, it is thought that a hydrophilic polymer is diffused to the outside of floc and it slips out of it from floc by diffusion of the solvent from a film production undiluted solution and invasion of nonsolvent in that case although floc generates after the nucleation of a polysulfone system polymer. Then, a hydrophilic polymer will be condensed by the generated floc front face, if the coagulation of floc is made to complete before the hydrophilic polymer has fallen out completely. Therefore, in order to make a floc front face condense PVP by desirable concentration, it is necessary to control the diffusion rate of PVP in the floc in a generation process, and can control by the factor which the following explains in full detail.

[0015] The first controlling factor is the molecular weight of PVP in a film production undiluted solution. That is, when the molecular weight of PVP is too small, before generation of floc is completed, PVP is promptly diffused out of floc and is not condensed by the floc front face by desired concentration. On the contrary, when molecular weight is large, since the diffusion rate of PVP becomes slow since a tangle of a polysulfone system polymer becomes large, it is easy to be condensed, and it becomes firm becoming after condensation entangled with a polysulfone system polymer so that molecular weight is large, the elution from a front face is also stopped. Therefore, desirable molecular weight is 200,000-500,000, if larger than this, the viscosity of a film production undiluted solution will be too high, and spinning nature will worsen. Still more desirable molecular weight is 300,000-400,000.

[0016] The second controlling factor is the presentation of a hollow agent. A hollow agent may contain PVP in coincidence, although the presentation which can control the generation rate of floc and the diffusion rate of PVP in a film production undiluted solution is desirable and the water solution of a solvent is used. This is because a floc front face can be made to condense PVP by desired concentration if generation of floc is made to complete after PVP in a hollow agent has formed PVP which is going to diffuse promptly and it is going to diffuse out of a film production undiluted solution into a film production undiluted solution, and sufficient concentration balance immediately after the regurgitation. Therefore, the one where a diffusion rate is larger than PVP in a film production undiluted solution is desirable, and the thing of smaller molecular weight is used. Desirable molecular weight is 0.5-50,000. Moreover, the diffusion rate of PVP in a film production undiluted solution is delayable as an addition is increased, but if an addition increases, a membranous coagulation rate will become slow and spinning nature will worsen. Therefore, a desirable addition is 10 - 30 % of the weight.

[0017] The solvent added by the hollow agent is used in order to control the penetrable ability of the generation rate of floc, and the film, and it is a **** undiluted solution, the same, or a different presentation, and the generation rate of floc becomes slow and, moreover, can enlarge particle diameter as an addition is increased. The addition of a solvent desirable for terminating generation of floc, after PVP diffused from a hollow agent and PVP diffused from floc have fully reached the concentration balance is 0 - 60 % of the weight, and the film formed when there were many additions more than this will penetrate albumin. It is 30 - 50 % of the weight still more preferably.

[0018] The third controlling factor is temperature. An above-mentioned film production

undiluted solution and an above-mentioned hollow agent are breathed out by coincidence from the spinneret which has an annular orifice, and are drawn after air transit and into a coagulation bath. In this case, the diffusion rate of PVP is controllable also by the temperature of a film production undiluted solution, a hollow agent, and the air transit section. Diffusion of PVP can be sped up so that these are made into an elevated temperature, but since the viscosity of a film production undiluted solution will fall and a membranous coagulation rate will also become slow if too high, spinning nature worsens. The diffusion rate of PVP is delayable so that it is made low temperature on the contrary, but if too low, membranous coagulation will be quick and PVP will not be condensed by the floc surface layer. Therefore, the desirable temperature of a film production undiluted solution is 30-80 degrees C, and is 35-60 degrees C still more preferably. The temperature of a hollow agent presupposes that it is the same as that of a film production undiluted solution. Moreover, if it differs from the temperature of a film production undiluted solution extremely, since spinning nature will worsen, the temperature of the air transit section is set as 30-80 degrees C like a film production undiluted solution, and is 35-60 degrees C still more preferably. A coagulation bath is used the making a solvent and excessive PVP remove in addition to making membranous coagulation complete purpose, and desirable temperature is 40-60 degrees C.

[0019] Thus, it inserts in a cassette, after rolling round to skein the hollow fiber made to solidify and cutting it to fixed length. A hot water shower is made to **, the inside, the outside, and the cross-section section of a hollow filament are washed, and still more nearly excessive PVP is made to remove from the cutting plane upper part of a bundle. If a glycerol water solution is made to adhere finally and it dries, the hollow fiber of this invention will be obtained.

[0020]

[Example] Next, although an example explains this invention concretely, this invention is not limited at all by them. In addition, many numeric values used in the example are measured in the following procedures.

(Diameter of floc) The photograph (scale factor; 70,000 times) of a freeze fracture side was taken with the field emission-type scanning electron microscope, and the average diameter of the floc of the outermost layer of a compact layer was computed.

(PVP concentration in the film) a hollow filament -- a stream -- it was immersed in inside (water temperature; 15-20 degrees C) one whole day and night, and the adhering glycerol was washed. It asked for the nitrogen concentration in the film by ********** for having carried out the bone dry at 105 degrees C, and converted into PVP concentration.

[0021] (PVP concentration on the front face of floc) PVP concentration was computed by having asked for the average concentration of the nitrogen to a floc surface depth of 6nm, and a sulfur atom, and having substituted this for the formula (3) using X linear-light electron-spectrum measuring device (PHI-5400 mold). The following procedures performed the preparation of a sample.

Internal surface: It was cut open so that an internal surface might expose a hollow filament with a die length of 5mm, and it fixed that several clearances cannot be found in a sample base.

Outside surface: It was cut open so that an internal surface might expose a hollow filament with a die length of 5mm, and it fixed that several clearances cannot be found in a sample base.

Cross-section section: The freeze fracture of the hollow fiber bundled dozens of was carried out, and it fixed to the sample base so that a torn surface might become upward.

[0022] (Adhesion of the platelet to a hollow fiber) It considered as the index of activation of the amount of adhesion on the front face of the film. Bundle ten hollow fibers with a die length of

15cm, create a small module, and this module is made to pass heparinize fresh blood for 15 minutes in linear velocity 1.0 cm/sec, and the physiological saline was continuously passed for 1 minute. Next, the quantum of the lactate dehydrogenase emitted from the platelet which carried out beating of the hollow filament, carried out ultrasonic irradiation in the physiological saline which contains a triton X-100 0.5%, and adhered to the film front face was carried out. Measurement of enzyme activity used the LDH mono-test kit (Boehringer Mannheim and made in Yamanouchi).

[0023] (Adsorption of the plasma protein to a hollow fiber) 100 hollow fibers with a die length of 20cm were bundled, and the small module was created. After introducing into this module the heparinize cow plasma (heparin 5000 IU/l, protein concentration 6.0 g/dl) warmed at 37 degrees C by linear velocity 1.0 cm/sec and performing an ultrafiltration for 240 minutes in differential pressure 50mmHg between film, the physiological saline washed for 1 minute. Next, beating of the hollow fiber was carried out and the quantum of the plasma protein stirred and extracted in the physiological saline which contains lauryl acid sodium 1.0% was carried out. Measurement of protein concentration used BCA protein assay (made in Pierce).

[0024] (Ovalbumin transmissometry in a drainage system) 100 hollow fibers with a die length of 20cm were bundled, and the small module was created. The ovalbumin water solution (250 ppm) warmed at 37 degrees C was introduced into this module by linear velocity 1.0 cm/sec, and the ultrafiltration was performed for 30 minutes in differential pressure 25mmHg between film. Permeability was computed by having measured the absorbance of the obtained filtrate and former liquid on the wavelength of 280nm, and having substituted for the following formula (4).

[0025]

[Formula 2]

[0026] (Albumin transmission in a cow plasma system, and UFR measurement) 100 hollow fibers with a die length of 20cm were bundled, and the small module was created. This module was made to pass the heparinize cow plasma (heparin 5000 IU/l, protein concentration 6.0 g/dl) warmed at 37 degrees C by linear velocity 1.0 cm/sec, and the ultrafiltration was performed to it for 60 minutes in differential pressure 50mmHg between film. After the transmission of albumin extracted filtrate after dipping initiation in the 30th minute and carried out the quantum of the obtained albumin concentration of filtrate and former liquid, it computed transmission by having substituted it for the following formula (5). Measurement of albumin concentration used A/GB-Test Wako (Wako Pure Chem make). UFR measurement extracted filtrate in the 5, 30, and 60th minute, and measured and computed weight.

[0027]

[Formula 3]

[0028] (Effluent) 1.5g of hollow fibers was put into 150ml of water, and it heated at 70 degrees C for 1 hour. The ultraviolet-rays absorbance was measured in the range with a wavelength of 220-350nm about this supernatant.

[0029] (Example 1) The polysulfone (product made from AMCO-- 1700) 16 section and the PVP(BASF [A.G.] make: K-90, molecular weight 360,000) 4 section were added in the

DMAC80 section, it stirred and dissolved at 50 degrees C for 8 hours, and the film production undiluted solution was obtained. Next, the DMAC45 section and the water 55 section were mixed and the hollow agent was obtained. After passing the inside of the 60-degree C coagulation bath in which the air transit section which kept it warm at 50 degrees C was made to breathe out the film production undiluted solution which kept it warm at 50 degrees C, and a hollow agent to coincidence from the spinneret which has 0.3mm of dies bodies, and an annular orifice with a bore of 0.2mm, and the discharge part installed them caudad 45cm, it rolled round to skein. Washed the 80-degree C hot water shower over 2 hours after cutting from the cutting plane upper part of a bundle, the glycerol water solution was made to adhere, and the vacuum drying was carried out. The obtained hollow fiber had neither degradation of membraneous ability, nor activation of a platelet. A measurement result is shown in Table -1.

[0030] (Example 2) The conditions of an example 1 were followed except having used the hollow agent which consists of the DMAC30 section, the PVP(K-15, molecular weight 40,000) 30 section, and the water 40 section. The obtained hollow fiber had neither degradation of membraneous ability, nor activation of a platelet. A measurement result is shown in Table -1.

[0031] (Example 1 of a comparison) The conditions of an example were followed using the hollow agent which consists of the DMAC25 section and the water 75 section except having kept warm further the temperature of a film production undiluted solution and the air transit section at 23 degrees C. The obtained hollow fiber had intense degradation of membraneous ability, and the platelet was activated. A measurement result is shown in Table -1.

[0032]

[Table 1]

[0033]

[Effect of the Invention] The constituent of this invention has neither degradation of membraneous ability, nor activation of a platelet, and is useful as permselective membrane for hemodialysis.

TECHNICAL FIELD

[Industrial Application] This invention relates to the hollow filament-like polysulfone system permselective membrane used in the plasma analysis field.

PRIOR ART

[Description of the Prior Art] Conventionally, in the field of hemodialysis, some hollow fibers made [are easy to carry out control of the membranous dialysis engine performance at the time of film production, and] from a synthetic polymer since it says that it excels in biocompatibility are put in practical use. As film which combines a mechanical strength and chemical stability also in it, a polysulfone system hollow fiber is beginning to be used widely. However, since surface hydrophilic properties run short remarkably when a film material consists of a polysulfone system polymer independent, adsorption of a plasma protein tends to take place. Consequently, the performance degradation of the film by the blinding in the membranous hole section will happen. And when hydrophilic properties ran short, the omission of the air bubbles at the time of a priming was bad, and in order that the air bubbles which remained into the film might slip out gradually into blood and might activate a platelet, there was a fault of having started platelet adhesion and being easy to result in plasma coagulation. Thus, it is difficult to obtain the hemodialysis film and it was possible to carry out hydrophilization by the approach of blending a hydrophilic polymer to a polysulfone system polymer a polysulfone system polymer independent.

[0003] Although various approaches have mainly been considered for the purpose of permeable improvement about the hydrophilization of a polysulfone system polymer, the following two examples are indicated as an approach of controlling the elution of a hydrophilic polymer to the minimum, and acquiring sufficient hydrophilic property. Although the film with which a hydrophilic polymer exists only in a membranous compact layer side is indicated by JP,62-38205,A, it is not indicated to the medical-application way. Furthermore, the film with which the hydrophilic polymer was unevenly distributed in the film near the internal surface of a hollow fiber only at one side is indicated by JP,4-300636,A. However, by this film, since the hydrophilic polymer is unevenly distributed only in membranous one side, it is thought that taking place and winding [adsorption of a plasma protein]-in other part performance degradation tends to happen, and the omission of air bubbles is also bad, therefore tends to cause activation of a platelet.

EFFECT OF THE INVENTION

[Effect of the Invention] The constituent of this invention has neither degradation of membraneous ability, nor activation of a platelet, and is useful as permselective membrane for hemodialysis.

TECHNICAL PROBLEM

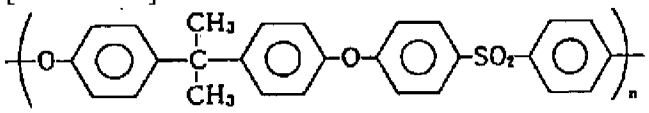
[Problem(s) to be Solved by the Invention] This invention offers the polysulfone system permselective membrane to which neither performance degradation nor activation of a platelet can take place easily.

MEANS

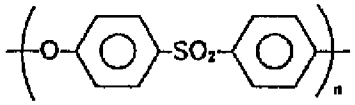
[Means for Solving the Problem] It found out that neither membranous performance degradation nor activation of a platelet could start easily the polysulfone system permselective membrane obtained by this invention as a result of inquiring wholeheartedly, in order to solve said technical problem since hydrophilization of all the floc front faces that form the film is carried out to homogeneity. Although the first material which forms the film of this invention is a polysulfone system polymer and it is the following chemical formula (1) or the polymer shown by (2), the so-called denaturation polysulfone into which the functional group and alkyl group of aromatic series were introduced is sufficient, and there is especially no limitation.

[0006]

[Formula 1]



..... (1)



..... (2)

[0007] The second material is a hydrophilic polymer and a polyvinyl pyrrolidone is mentioned as an example of representation that what is necessary is just a polysulfone system polymer and the compatibility-ized thing. Although a copolymer, a polyethylene glycol, etc. of vinyl pyrrolidone and other vinyl system monomers are mentioned to others, the hydrophilic polymer is condensed by uniform concentration in the front face of each floc.

[0008] Since the concentration of a hydrophilic polymer runs short of the hydrophilic properties on the front face of floc if it is too low, adsorption of a plasma protein starts, membranous performance degradation is caused, and the omission of the air bubbles at the time of a priming is bad, and becomes easy to cause activation of a platelet. Since a tangle in a polysulfone system polymer will become inadequate and an underwater elution volume will increase on the contrary if concentration is too high, it is not desirable as a medical-application way. Therefore, the

hydrophilic polymer concentration on the front face of floc has 25 - 50 desirable % of the weight, and its 25 - 35 % of the weight is still more desirable. The hydrophilic polymer concentration used here scans the floc front face exposed to a hollow filament front face through an X-ray, and is the value the obtained photoelectron spectrum asked for the average concentration of a ****** element, and computed by having assigned it to the following type (3).

[0009]

[Formula 1]

$$\text{親水性ポリマー濃度（重量%）} = \frac{C_1 \times M_1}{C_1 \times M_1 + C_2 \times M_2} \times 100 \quad \cdots\cdots (3)$$

C1 : In the case of nitrogen atom (%) and concentration, and a polyethylene glycol, content **** of a nitrogen-containing hydrophilic-property polymer is the carbon atom concentration (%) of a carbonyl group.

C2 : Sulfur atom concentration (%)

M1 : Molecular weight M2 of the repeat unit of a hydrophilic polymer : Molecular weight of the repeat unit of a polysulfone system polymer [0010] The film of this invention is the aggregate of such floc, and has supporters for the compact layer in the other part in the contact surface side with blood. A compact layer is a part which determines penetrable ability, and can mention the magnitude of the floc which forms the compact layer as an important factor. The diameter of the floc which generally forms the compact layer is small, and membranous penetrable ability becomes low, so that it moreover gathers to nectar. On the contrary, even if too large, the albumin which is a useful plasma protein penetrates and it is not desirable as hemofiltration film.

[0011] Although the beta2-micro globulin (molecular weight: 11,800) made into the causative agent for the improvement of a dialysis amyloid symptom is made to fully penetrate, most albumin (molecular weight: 67,000) needs to control the magnitude of the floc of a compact layer by the latest hemofiltration therapy for the film which has the fractionation nature which is not made to penetrate to be called for, and make such penetrable ability discover. The magnitude of floc is computed as an average diameter from the electron microscope photograph of the hollow filament cross-section section, and 10-100nm of diameters is 10-50nm preferably.

[0012] Although the transmission of the ovalbumin (molecular weight: 47,000) in a drainage system is 40 - 80% and, as for the hemodialysis film of this invention, the transmission of the albumin in a cow plasma system has the description of 1.0% or less, these are equivalent to the level of [transmission / of a beta2-micro globulin] 0.3% or less in the transmission of 60 - 70%, and albumin in actual hemodialysis. Although supporters are governing the membranous mechanical strength and ** can be considered, about the magnitude and its set gestalt of the floc in supporters, there is especially no limitation that sufficient film reinforcement should just be obtained.

[0013] Next, the case where a polyvinyl pyrrolidone (henceforth "PVP") is used for a hydrophilic polymer is explained as an example of the embodiment of a hollow fiber which has the above-mentioned description. As a presentation of a film production undiluted solution, PVP consists [a polysulfone system polymer] of 2 - 8 % of the weight, and these solvents ten to 20% of the weight. That what is necessary is just what can dissolve a polysulfone system polymer and a polyvinyl pyrrolidone, N,N-dimethylacetamide (henceforth "DMAC"), N.N-dimethylformamide, a N-methyl-2-pyrrolidone, dimethyl sulfoxide, etc. are enumerated, and a solvent can mix and use these at a rate of independence or arbitration. Furthermore, water may be added as nonsolvent of a polysulfone system polymer to extent in which a polymer does not

deposit.
[0014] In a film production process, it is thought that a hydrophilic polymer is diffused to the outside of floc and it slips out of it from floc by diffusion of the solvent from a film production undiluted solution and invasion of nonsolvent in that case although floc generates after the nucleation of a polysulfone system polymer. Then, a hydrophilic polymer will be condensed by the generated floc front face, if the coagulation of floc is made to complete before the hydrophilic polymer has fallen out completely. Therefore, in order to make a floc front face condense PVP by desirable concentration, it is necessary to control the diffusion rate of PVP in the floc in a generation process, and can control by the factor which the following explains in full detail.
[0015] The first controlling factor is the molecular weight of PVP in a film production undiluted solution. That is, when the molecular weight of PVP is too small, before generation of floc is completed, PVP is promptly diffused out of floc and is not condensed by the floc front face by desired concentration. On the contrary, when molecular weight is large, since the diffusion rate of PVP becomes slow since a tangle of a polysulfone system polymer becomes large, it is easy to be condensed, and it becomes firm becoming after condensation entangled with a polysulfone system polymer so that molecular weight is large, the elution from a front face is also stopped. Therefore, desirable molecular weight is 200,000-500,000, if larger than this, the viscosity of a film production undiluted solution will be too high, and spinning nature will worsen. Still more desirable molecular weight is 300,000-400,000.
[0016] The second controlling factor is the presentation of a hollow agent. A hollow agent may contain PVP in coincidence, although the presentation which can control the generation rate of floc and the diffusion rate of PVP in a film production undiluted solution is desirable and the water solution of a solvent is used. This is because a floc front face can be made to condense PVP by desired concentration if generation of floc is made to complete after PVP in a hollow agent has formed PVP which is going to diffuse promptly and it is going to diffuse out of a film production undiluted solution into a film production undiluted solution, and sufficient concentration balance immediately after the regurgitation. Therefore, the one where a diffusion rate is larger than PVP in a film production undiluted solution is desirable, and the thing of smaller molecular weight is used. Desirable molecular weight is 0.5-50,000. Moreover, the diffusion rate of PVP in a film production undiluted solution is delayable as an addition is increased, but if an addition increases, a membranous coagulation rate will become slow and spinning nature will worsen. Therefore, a desirable addition is 10 - 30 % of the weight.
[0017] The solvent added by the hollow agent is used in order to control the penetrable ability of the generation rate of floc, and the film, and it is a **** undiluted solution, the same, or a different presentation, and the generation rate of floc becomes slow and, moreover, can enlarge particle diameter as an addition is increased. The addition of a solvent desirable for terminating generation of floc, after PVP diffused from a hollow agent and PVP diffused from floc have fully reached the concentration balance is 0 - 60 % of the weight, and the film formed when there were many additions more than this will penetrate albumin. It is 30 - 50 % of the weight still more preferably.
[0018] The third controlling factor is temperature. An above-mentioned film production undiluted solution and an above-mentioned hollow agent are breathed out by coincidence from the spinneret which has an annular orifice, and are drawn after air transit and into a coagulation bath. In this case, the diffusion rate of PVP is controllable also by the temperature of a film production undiluted solution, a hollow agent, and the air transit section. Diffusion of PVP can

be sped up so that these are made into an elevated temperature, but since the viscosity of a film production undiluted solution will fall and a membranous coagulation rate will also become slow if too high, spinning nature worsens. The diffusion rate of PVP is delayable so that it is made low temperature on the contrary, but if too low, membranous coagulation will be quick and PVP will not be condensed by the floc surface layer. Therefore, the desirable temperature of a film production undiluted solution is 30-80 degrees C, and is 35-60 degrees C still more preferably. The temperature of a hollow agent presupposes that it is the same as that of a film production undiluted solution. Moreover, if it differs from the temperature of a film production undiluted solution extremely, since spinning nature will worsen, the temperature of the air transit section is set as 30-80 degrees C like a film production undiluted solution, and is 35-60 degrees C still more preferably. A coagulation bath is used the making a solvent and excessive PVP remove in addition to making membranous coagulation complete purpose, and desirable temperature is 40-60 degrees C.

[0019] Thus, it inserts in a cassette, after rolling round to skein the hollow fiber made to solidify and cutting it to fixed length. A hot water shower is made to **, the inside, the outside, and the cross-section section of a hollow filament are washed, and still more nearly excessive PVP is made to remove from the cutting plane upper part of a bundle. If a glycerol water solution is made to adhere finally and it dries, the hollow fiber of this invention will be obtained.

EXAMPLE

[Example] Next, although an example explains this invention concretely, this invention is not limited at all by them. In addition, many numeric values used in the example are measured in the following procedures.

(Diameter of floc) The photograph (scale factor; 70,000 times) of a freeze fracture side was taken with the field emission-type scanning electron microscope, and the average diameter of the floc of the outermost layer of a compact layer was computed.

(PVP concentration in the film) a hollow filament -- a stream -- it was immersed in inside (water temperature; 15-20 degrees C) one whole day and night, and the adhering glycerol was washed. It asked for the nitrogen concentration in the film by ********** for having carried out the bone dry at 105 degrees C, and converted into PVP concentration.

[0021] (PVP concentration on the front face of floc) PVP concentration was computed by having asked for the average concentration of the nitrogen to a floc surface depth of 6nm, and a sulfur atom, and having substituted this for the formula (3) using X linear-light electron-spectrum measuring device (PHI-5400 mold). The following procedures performed the preparation of a sample.

Internal surface: It was cut open so that an internal surface might expose a hollow filament with a die length of 5mm, and it fixed that several clearances cannot be found in a sample base.

Outside surface: It was cut open so that an internal surface might expose a hollow filament with a die length of 5mm, and it fixed that several clearances cannot be found in a sample base.

Cross-section section: The freeze fracture of the hollow fiber bundled dozens of was carried out, and it fixed to the sample base so that a torn surface might become upward.

[0022] (Adhesion of the platelet to a hollow fiber) It considered as the index of activation of the amount of adhesion on the front face of the film. Bundle ten hollow fibers with a die length of 15cm, create a small module, and this module is made to pass heparinize fresh blood for 15

minutes in linear velocity 1.0 cm/sec, and the physiological saline was continuously passed for 1 minute. Next, the quantum of the lactate dehydrogenase emitted from the platelet which carried out beating of the hollow filament, carried out ultrasonic irradiation in the physiological saline which contains a triton X-100 0.5%, and adhered to the film front face was carried out. Measurement of enzyme activity used the LDH mono-test kit (Boehringer Mannheim and made in Yamanouchi).

[0023] (Adsorption of the plasma protein to a hollow fiber) 100 hollow fibers with a die length of 20cm were bundled, and the small module was created. After introducing into this module the heparinize cow plasma (heparin 5000 IU/l, protein concentration 6.0 g/dl) warmed at 37 degrees C by linear velocity 1.0 cm/sec and performing an ultrafiltration for 240 minutes in differential pressure 50mmHg between film, the physiological saline washed for 1 minute. Next, beating of the hollow fiber was carried out and the quantum of the plasma protein stirred and extracted in the physiological saline which contains lauryl acid sodium 1.0% was carried out. Measurement of protein concentration used BCA protein assay (made in Pierce).

[0024] (Ovalbumin transmissometry in a drainage system) 100 hollow fibers with a die length of 20cm were bundled, and the small module was created. The ovalbumin water solution (250 ppm) warmed at 37 degrees C was introduced into this module by linear velocity 1.0 cm/sec, and the ultrafiltration was performed for 30 minutes in differential pressure 25mmHg between film. Permeability was computed by having measured the absorbance of the obtained filtrate and former liquid on the wavelength of 280nm, and having substituted for the following formula (4).

[0025]

[Formula 2]

$$\text{透過率（％）} = \frac{\text{濾液の吸光度}}{\text{元液の吸光度}} \times 100 \quad \cdots\cdots (4)$$

[0026] (Albumin transmission in a cow plasma system, and UFR measurement) 100 hollow fibers with a die length of 20cm were bundled, and the small module was created. This module was made to pass the heparinize cow plasma (heparin 5000 IU/l, protein concentration 6.0 g/dl) warmed at 37 degrees C by linear velocity 1.0 cm/sec, and the ultrafiltration was performed to it for 60 minutes in differential pressure 50mmHg between film. After the transmission of albumin extracted filtrate after dipping initiation in the 30th minute and carried out the quantum of the obtained albumin concentration of filtrate and former liquid, it computed transmission by having substituted it for the following formula (5). Measurement of albumin concentration used A/GB-Test Wako (Wako Pure Chem make). UFR measurement extracted filtrate in the 5, 30, and 60th minute, and measured and computed weight.

[0027]

[Formula 3]

$$\text{透過率（％）} = \frac{\text{濾液のアルブミン濃度}}{\text{元液のアルブミン濃度}} \times 100 \quad \cdots\cdots (5)$$

[0028] (Effluent) 1.5g of hollow fibers was put into 150ml of water, and it heated at 70 degrees C for 1 hour. The ultraviolet-rays absorbance was measured in the range with a wavelength of 220-350nm about this supernatant.

[0029] (Example 1) The polysulfone (product made from AMCO-- 1700) 16 section and the PVP(BASF [A.G.] make: K-90, molecular weight 360,000) 4 section were added in the DMAC80 section, it stirred and dissolved at 50 degrees C for 8 hours, and the film production

undiluted solution was obtained. Next, the DMAC45 section and the water 55 section were mixed and the hollow agent was obtained. After passing the inside of the 60-degree C coagulation bath in which the air transit section which kept it warm at 50 degrees C was made to breathe out the film production undiluted solution which kept it warm at 50 degrees C, and a hollow agent to coincidence from the spinneret which has 0.3mm of dies bodies, and an annular orifice with a bore of 0.2mm, and the discharge part installed them caudad 45cm, it rolled round to skein. Washed the 80-degree C hot water shower over 2 hours after cutting from the cutting plane upper part of a bundle, the glycerol water solution was made to adhere, and the vacuum drying was carried out. The obtained hollow fiber had neither degradation of membraneous ability, nor activation of a platelet. A measurement result is shown in Table -1.

[0030] (Example 2) The conditions of an example 1 were followed except having used the hollow agent which consists of the DMAC30 section, the PVP(K-15, molecular weight 40,000) 30 section, and the water 40 section. The obtained hollow fiber had neither degradation of membraneous ability, nor activation of a platelet. A measurement result is shown in Table -1.

[0031] (Example 1 of a comparison) The conditions of an example were followed using the hollow agent which consists of the DMAC25 section and the water 75 section except having kept warm further the temperature of a film production undiluted solution and the air transit section at 23 degrees C. The obtained hollow fiber had intense degradation of membraneous ability, and the platelet was activated. A measurement result is shown in Table -1.

[0032]

[Table 1]

表－1	実施例1	実施例2	比較例1
膜中のＰＶＰ濃度 (%)	6.8	7.0	6.2
凝集粒子表面のＰＶＰ濃度(%)			
内表面	33	38	20
外表面	35	40	19
断　面	31	40	20
凝集粒子直径(nm)	40	51	31
血小板粘着量 (LDH-unit/cm-HF)	8.3	4.1	105.8
血漿蛋白吸着量 (mg/g-HF)	2.8	2.1	66.4
水系オボアルブミン透過率　(%)	67.5	73.8	61.1
牛血漿系アルブミン透過率　(%)	0.3	0.8	0.7
牛血漿系ＵＦＲ (ml/mmHg·hr·m²)			
5分目	41	43	26
30分目	41	44	21
60分目	40	43	18
溶出物 (ABS.max)	0.055	0.084	0.042

[Translation done.]